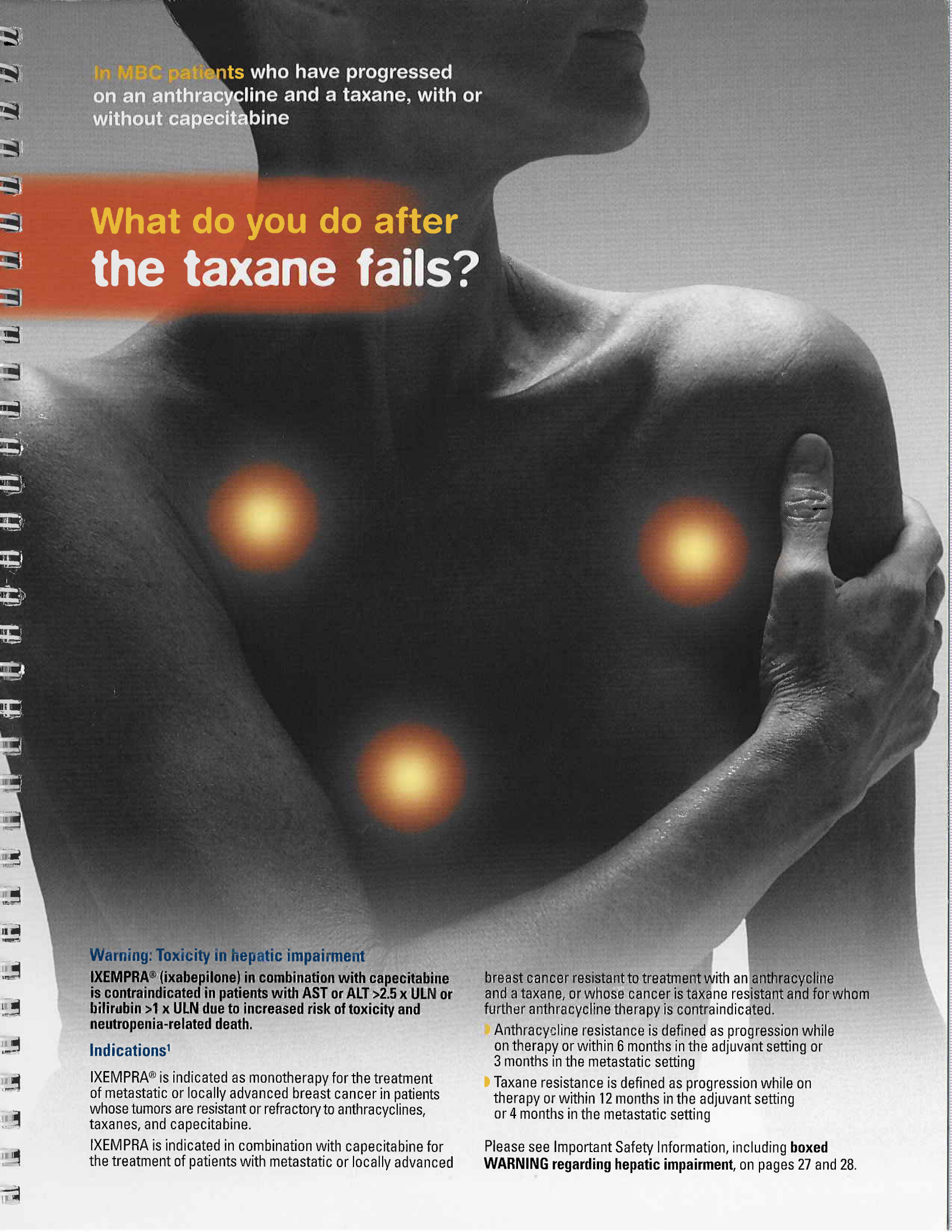


In MBC patients who have progressed on an anthracycline and a taxane, with or without capecitabine

What do you do after the taxane fails?

Warning: Toxicity in hepatic impairment

IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death.

Indications[1]

IXEMPRA® is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

IXEMPRA is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

- Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting
- Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

3 years since FDA approval, thousands of patients treated*

Offer IXEMPRA® (ixabepilone)

Safety Information: Contraindications

IXEMPRA® (ixabepilone) is contraindicated in patients:

- with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives, such as polyoxyethylated castor oil
- who have a baseline neutrophil count <1500 cells/mm^3 or a platelet count <100,000 cells/mm^3
- in combination with capecitabine, when AST or ALT is >2.5 × ULN or bilirubin is >1 × ULN due to increased risk of toxicity and neutropenia-related death

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

Cremophor is a registered trademark of BASF AG.

*14,800 patients. Source: IntelliView data from IntrinsiQ, LLC. Research market share data: 2007-2010. Proprietary and nonpublished data, available for purchase at: http://www.intrinsiq.com. Accessed August 23, 2010.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Monotherapy: In MBC patients progressing on an anthracycline, a taxane, and capecitabine, based on demonstrated efficacy and safety, including patients in the 2nd and 3rd line setting

Combination therapy with capecitabine: In MBC patients progressing on an anthracycline and a taxane, based on demonstrated efficacy and safety, including patients in the 1st and 2nd line settings

Uses of IXEMPRA® (ixabepilone), a non-taxane chemotherapy, include:

- 2nd and 3rd line monotherapy or
- 1st or 2nd line therapy in combination with capecitabine

Metastatic[2]

First Line	Second Line	Third Line +
MONOTHERAPY	**MONOTHERAPY**	**MONOTHERAPY**
	IXEMPRA (after A + T + C)	**IXEMPRA** (after A + T + C)
COMBINATION	**COMBINATION**	**COMBINATION**
IXEMPRA + capecitabine (after A and T)	**IXEMPRA + capecitabine** (after A and T)	**IXEMPRA + capecitabine** (after A and T)

Legend: A=Anthracyclines; T=Taxanes; C=Capecitabine.

Safety Information: Hypersensitivity reaction

- Premedicate with an H_1 and an H_2 antagonist approximately 1 hour before IXEMPRA® (ixabepilone) infusion and observe for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started
- Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H_1 and H_2 antagonists, and extension of the infusion time should be considered

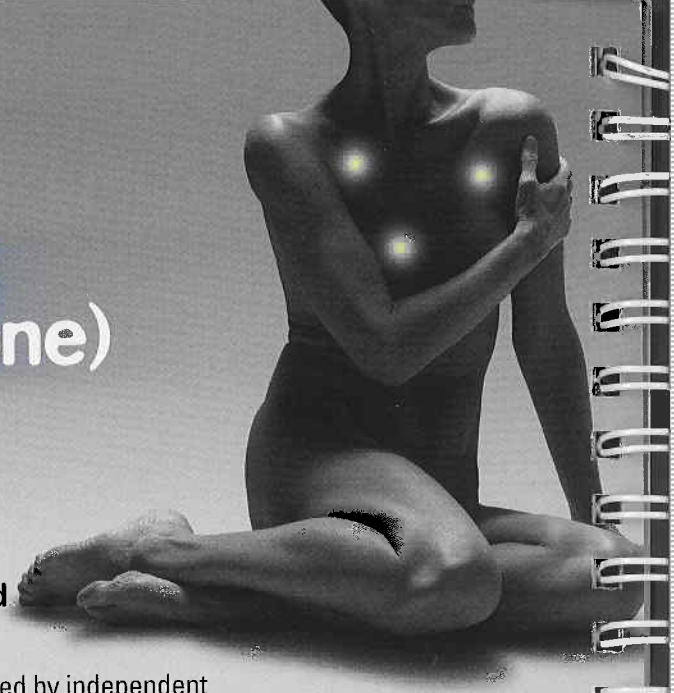
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection

In MBC patients who have progressed on an anthracycline, a taxane, and capecitabine

After the taxane fails,

Offer IXEMPRA® (ixabepilone)



IXEMPRA monotherapy: Study design[1,3]

Study 081: A single-arm, Phase II trial of IXEMPRA monotherapy in 126 patients whose tumors progressed on an anthracycline,* a taxane, and capecitabine

- Objective tumor response rate was the primary end point and was evaluated by independent radiologic and investigator review using Response Evaluation Criteria in Solid Tumors (RECIST)

RECIST criteria†	Abbreviated definition[4]
Complete response	Disappearance of all target lesions
Partial response	≥30% decrease in the sum of the longest diameter of target lesions
Progressive disease	≥20% increase in the sum of the longest diameter of target lesions
Stable disease	Neither sufficient shrinkage to qualify as partial response nor sufficient increase to qualify as progressive disease

†IXEMPRA clinical trial is based on RECIST criteria from *J Natl Cancer Inst* 2000.

- Resistance was defined as:
  - Disease progression while on treatment, or within 8 weeks of the last dose, in the metastatic setting
  - Recurrence within 6 months of the last dose in the adjuvant or neoadjuvant setting (for anthracyclines and taxanes)
  - Progression during or after discontinuation of trastuzumab for patients who were HER2+
- Patients received IXEMPRA® (ixabepilone) 40 mg/m² IV over 3 hours every 3 weeks

Safety Information: Pregnancy

- Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus

Safety Information: Cardiac adverse events

- Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group

*For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin were also eligible.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA® (ixabepilone) monotherapy: Results[1,3,5]

Demonstrated efficacy in objective tumor response with IXEMPRA monotherapy

Response	Response rate (n=113)	Median duration of response†
Objective tumor response	IRR=12.4%*† (95% CI, 6.9-19.9)	6.0 months (n=14, 95% CI, 5.0-7.6)
	IA=18.3%‡ (n=126, 95% CI, 11.9-26.1)	Not available (N/A)
Stable disease	50%§	4.9 months‖ (n=56, 95% CI, 3.8-6.9)
Stable disease ≥6 months	18.6% (95% CI, 11.9-27)	N/A
Progressive disease	32%§	N/A

*All responses were partial.
†As assessed by Independent Radiologic Review (IRR).
‡Investigator Assessment (IA).
§Confidence intervals not available.
‖Calculated for patients who achieved stable disease.

- Approximately 70% of patients received IXEMPRA® (ixabepilone) after initial taxane failure[5]
- Median time to response was 6.1 weeks (n=14, min-max 5.0-54.4)
- Stable disease was a prespecified analysis, not a prespecified end point
- 88% of patients received ≥2 chemotherapy regimens for metastatic disease
- 48% of patients received at least 3 lines of chemotherapy for metastatic disease
- Patients received a median of 4 cycles (range, 1-18) of IXEMPRA therapy

Safety Information: Adverse reactions

- Treatment-related nonhematologic adverse events (≥20%) included: peripheral sensory neuropathy 62% (grade 3/4: 14%), fatigue/asthenia 56% (grade 3/4: 13%), myalgia/arthralgia 49% (grade 3/4: 8%), alopecia 48% (grade 3/4: 0%), nausea 42% (grade 3/4: 2%), stomatitis/mucositis 29% (grade 3/4: 6%), vomiting 29% (grade 3/4: 1%), diarrhea 22% (grade 3/4: 1%), and musculoskeletal pain 20% (grade 3/4: 3%). Treatment-related hematologic abnormalities (>40%) in Studies 081 and 046 included: neutropenia, leukopenia, anemia, and thrombocytopenia. In Study 081, grade 3/4 hematologic adverse reactions included neutropenia 54%, leukopenia 49%, anemia 8%, and thrombocytopenia 7%

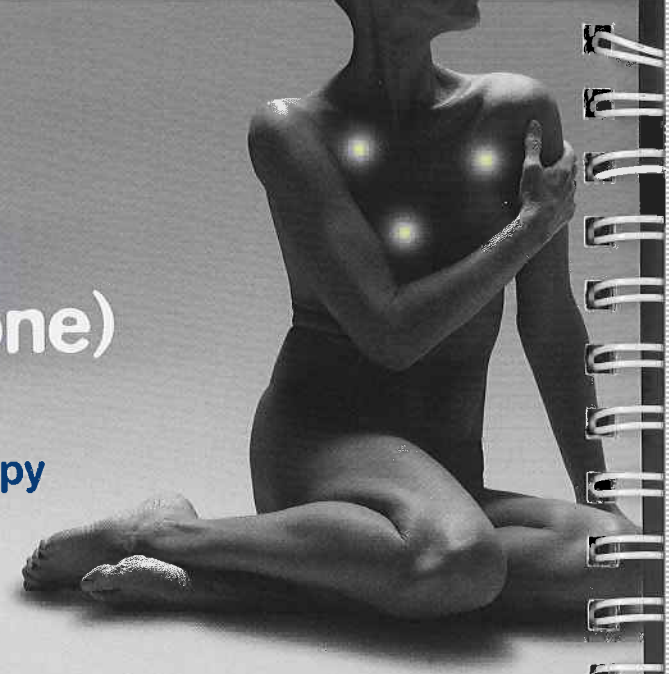
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™ (ixabepilone) for injection

In MBC patients who have progressed on an anthracycline, a taxane, and capecitabine

After the taxane fails,

Offer IXEMPRA® (ixabepilone)



The safety profile of IXEMPRA monotherapy

Study 081: Peripheral neuropathy[1]

Prior therapy with neurotoxic chemotherapy agents did not predict the development of neuropathy

- Peripheral neuropathy was common and primarily sensory

Peripheral neuropathy

	IXEMPRA as monotherapy
Preexisting baseline neuropathy (grade 1)*	27%
Peripheral neuropathy (all grades)*	63%
Peripheral neuropathy (grade 3/4)*	14%
Median number of cycles to onset of neuropathy (grade 3/4)	4

*Sensory and motor neuropathy combined.

Peripheral neuropathy is cumulative, generally reversible, and should be managed with dose adjustments and delays

- The median time to improvement of grade 3/4 neuropathy to baseline or grade 1 was 4.6 weeks
- Following dose reduction, 87% of patients had improvement or no worsening of their neuropathy
- Discontinuation due to neuropathy was 6%

Safety Information: Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA® (ixabepilone) should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

The safety profile of IXEMPRA® (ixabepilone) monotherapy

Study 081: Hematologic abnormalities[1]

Hematologic abnormalities

	IXEMPRA monotherapy (N=126)	
	Grade 3 (%)	Grade 4 (%)
Neutropenia*	31	23
Febrile neutropenia†	3	0
Leukopenia (WBC)	36	13
Anemia (Hgb)	6	2
Thrombocytopenia	5	2

*G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte-macrophage colony-stimulating factor) was used in 17% of patients who received IXEMPRA in Study 081.

†In clinical trials, febrile neutropenia was classified as a nonhematologic adverse event.

- Infection with neutropenia was reported in 5% of patients treated with IXEMPRA® (ixabepilone) as monotherapy

Safety Information: Myelosuppression

- IXEMPRA must not be administered to patients with a neutrophil count <1500 cells/mm^3
- Myelosuppression is dose-dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced
- Neutropenia-related death occurred in 0.4% of 240 patients treated with IXEMPRA as monotherapy

Safety Information: Hepatic impairment

- Assessment of hepatic function is recommended before initiation of IXEMPRA and periodically thereafter
- Patients with baseline AST or ALT >2.5 × ULN or bilirubin >1.5 × ULN experienced greater toxicity than patients with baseline AST or ALT ≤2.5 × ULN or bilirubin ≤1.5 × ULN when treated with IXEMPRA at 40 mg/m^2 as monotherapy in breast cancer studies
- With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent

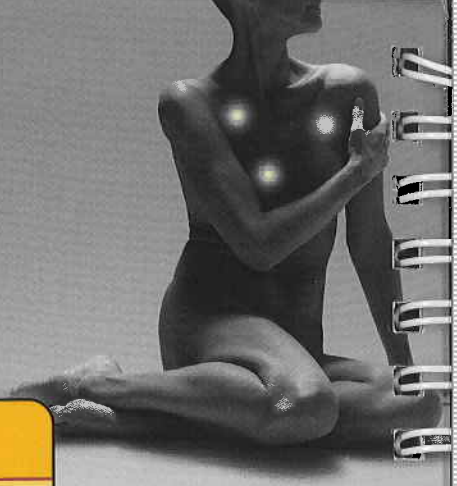
Safety Information: Potential for cognitive impairment from excipients

- IXEMPRA contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection



The safety profile of IXEMPRA® (ixabepilone) monotherapy

Study 081: Adverse reactions[1]

Adverse reactions occurring in ≥5% of patients

System organ class*/Preferred term	IXEMPRA (N=126) Total (%)	Grade 3/4 (%)
Infections and infestations		
Upper respiratory tract infection†	6	0
Blood and lymphatic system disorders		
Febrile neutropenia	3	3‡
Immune system disorders		
Hypersensitivity†	5	1‡
Metabolism and nutrition disorders		
Anorexia†	19	2‡
Dehydration†	2	1‡
Psychiatric		
Insomnia†	5	0
Nervous system disorders		
Peripheral neuropathy		
Sensory neuropathy†§	62	14
Motor neuropathy†	10	1‡
Headache	11	0
Taste disorder†	6	0
Dizziness	7	0
Eye disorders		
Lacrimation increased	4	0
Vascular disorders		
Hot flush†	6	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea†	9	1‡
Cough†	2	0

*System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS).

†A composite of multiple MedDRA Preferred Terms.

‡No grade 4 reports.

§Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyporeflexia, neuralgia, neuritis, neuropathy, neuropathy peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, pallanesthesia, peripheral sensory neuropathy, polyneuropathy, polyneuropathy toxic, and sensorimotor disorder. Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

The safety profile of IXEMPRA® (ixabepilone) monotherapy

Study 081: Adverse reactions[1] (continued)

Adverse reactions occurring in ≥5% of patients

System organ class*/Preferred term	IXEMPRA (N=126) Total (%)	Grade 3/4 (%)
Gastrointestinal disorders		
Nausea	42	2‡
Vomiting†	29	1‡
Stomatitis/mucositis†	29	6
Diarrhea†	22	1‡
Constipation	16	2‡
Abdominal pain†	13	2‡
Gastroesophageal reflux disease†	6	0
Skin and subcutaneous tissue disorders		
Alopecia†	48	0
Skin rash†	9	2‡
Nail disorder†	9	0
Palmar-plantar erythrodysesthesia syndrome†	8	2‡
Pruritus	6	1‡
Skin exfoliation†	2	0
Skin hyperpigmentation†	2	0
Musculoskeletal, connective tissue, and bone disorders		
Myalgia/arthralgia†	49	8‡
Musculoskeletal pain†	20	3‡
General disorders and administrative site conditions		
Fatigue/asthenia†	56	13
Edema†	9	1‡
Pyrexia	8	1‡
Pain†	8	3‡
Chest pain†	5	1‡
Investigations		
Weight decreased	6	0

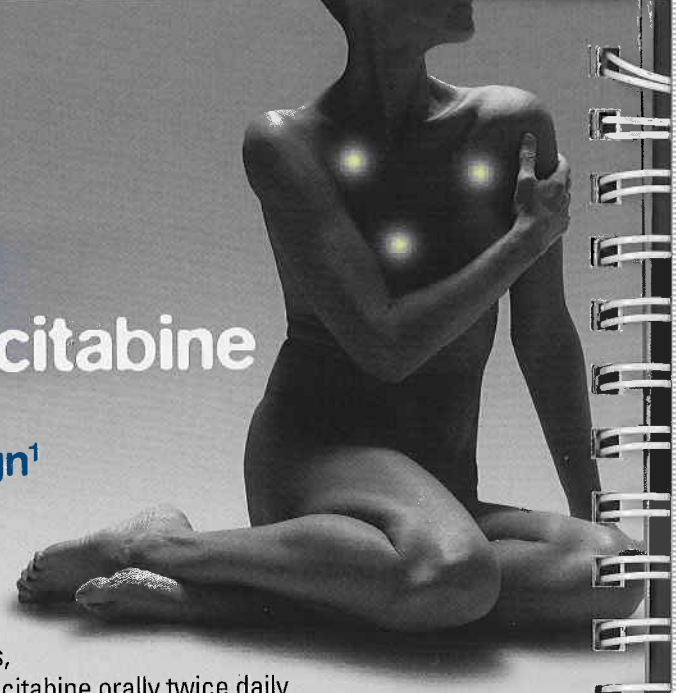
IXEMPRA™ (ixabepilone) for injection

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

In MBC patients who have progressed on an anthracycline and a taxane

After the taxane fails,

Offer IXEMPRA® (ixabepilone) + capecitabine



IXEMPRA combination therapy: Study design[1]

Study 046: A Phase III, open-label, multicenter, randomized trial of IXEMPRA combination therapy

- 375 patients received 40 mg/m² of ixabepilone intravenously over 3 hours every 3 weeks plus 1000 mg/m² of capecitabine orally twice daily x 2 weeks, followed by a 1 week rest period. 377 patients received 1250 mg/m² of capecitabine orally twice daily x 2 weeks, followed by a 1 week rest period
- Patients received a median of 5 cycles and 4 cycles in the combination and single-treatment groups, respectively
- Resistance criteria: Patients' tumors rapidly progressed or recurred on prior therapy
  - Tumors progressed within 3 months of the last anthracycline* dose in the metastatic setting –*or*– recurred within 6 months in the adjuvant or neoadjuvant setting
  - Tumors progressed within 4 months of the last taxane dose in the metastatic setting –*or*– recurred within 12 months in the adjuvant or neoadjuvant setting

End points:

Primary—Progression-free survival (PFS)†‡ determined by Independent Radiologic Review (IRR)
Secondary—Objective tumor response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST)

RECIST criteria§	Abbreviated definition[4]
Complete response	Disappearance of all target lesions
Partial response	≥30% decrease in the sum of the longest diameter of target lesions
Progressive disease	≥20% increase in the sum of the longest diameter of target lesions
Stable disease	Neither sufficient shrinkage to qualify as partial response nor sufficient increase to qualify as progressive disease

*For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin were also eligible.

†PFS was defined as time from randomization to radiologic progression, based on IRR of intent-to-treat population.

‡Patients were censored for PFS at the last date of tumor assessment prior to the start of subsequent therapy. In patients where independent review was not available, PFS was censored at the randomization date.

§IXEMPRA clinical trial is based on RECIST criteria from *J Natl Cancer Inst* 2000.

Warning: Toxicity in hepatic impairment

- **IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death**

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA® (ixabepilone) combination therapy: Results[1,6,7]

Study 046: IXEMPRA + capecitabine provided a statistically significant improvement in median PFS[1]

Phase III trial results (N=752)

	IXEMPRA + capecitabine (n=375)	Capecitabine (n=377)
Median PFS (HR=0.69*; 95% CI, 0.58-0.83) (*P*<0.0001)†	**5.7 months** (95% CI, 4.8-6.7)	**4.1 months** (95% CI, 3.1-4.3)
Objective tumor response (*P*<0.0001)†	**34.7%** (95% CI, 29.9-39.7)	**14.3%** (95% CI, 10.9-18.3)
Median duration of response‡[6]	**6.4 months** (95% CI, 5.6-7.1)	**5.6 months** (95% CI, 4.2-7.5)
Stable disease§[7]	**41%**	**46%**
Stable disease ≥6 months	**16%** (95% CI, 12.4-20.1)	**16%** (95% CI, 12.4-20.0)
Progressive disease§	**15%**	**27%**

*For the hazard ratio, a value less than 1.00 favors combination treatment.

†Stratified by visceral metastases in liver/lung, prior chemotherapy in the metastatic setting, and anthracycline resistance.

‡Calculated for all patients (n=130) who achieved an objective tumor response.

§Confidence intervals not available.

- Approximately 70% of patients received IXEMPRA® (ixabepilone) after initial taxane failure[1,6]
- More than double the ORR in the combination group in patients with metastatic or locally advanced breast cancer as evaluated using RECIST
- A 31% reduction in risk of disease progression (HR=0.69; 95% CI, 0.58-0.83; *P*<0.0001)*
- Stable disease was a prespecified analysis, not a prespecified end point
- There was no statistically significant difference in overall survival between treatment arms in 2 similarly designed studies
  - In the study described above, the median overall survivals were 12.9 months (95% CI, 11.5-14.2) in the combination therapy arm and 11.1 months (95% CI, 10.0-12.5) in the capecitabine alone arm (HR=0.90; 95% CI, 0.77-1.05; *P*=0.19)
  - In the second trial comparing IXEMPRA in combination with capecitabine versus capecitabine alone, conducted in 1221 patients pretreated with an anthracycline and taxane, the median overall survivals were 16.4 months (95% CI, 15.0-17.9) in the combination therapy arm and 15.6 months (95% CI, 13.9-17.0) in the capecitabine alone arm (HR=0.90; 95% CI, 0.78-1.03; *P*=0.12)

Safety Information: Contraindications

IXEMPRA is also contraindicated in patients:

- with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives such as polyoxyethylated castor oil
- who have a baseline neutrophil count <1500 cells/mm^3 or a platelet count <100,000 cells/mm^3

Cremophor is a registered trademark of BASF AG.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection

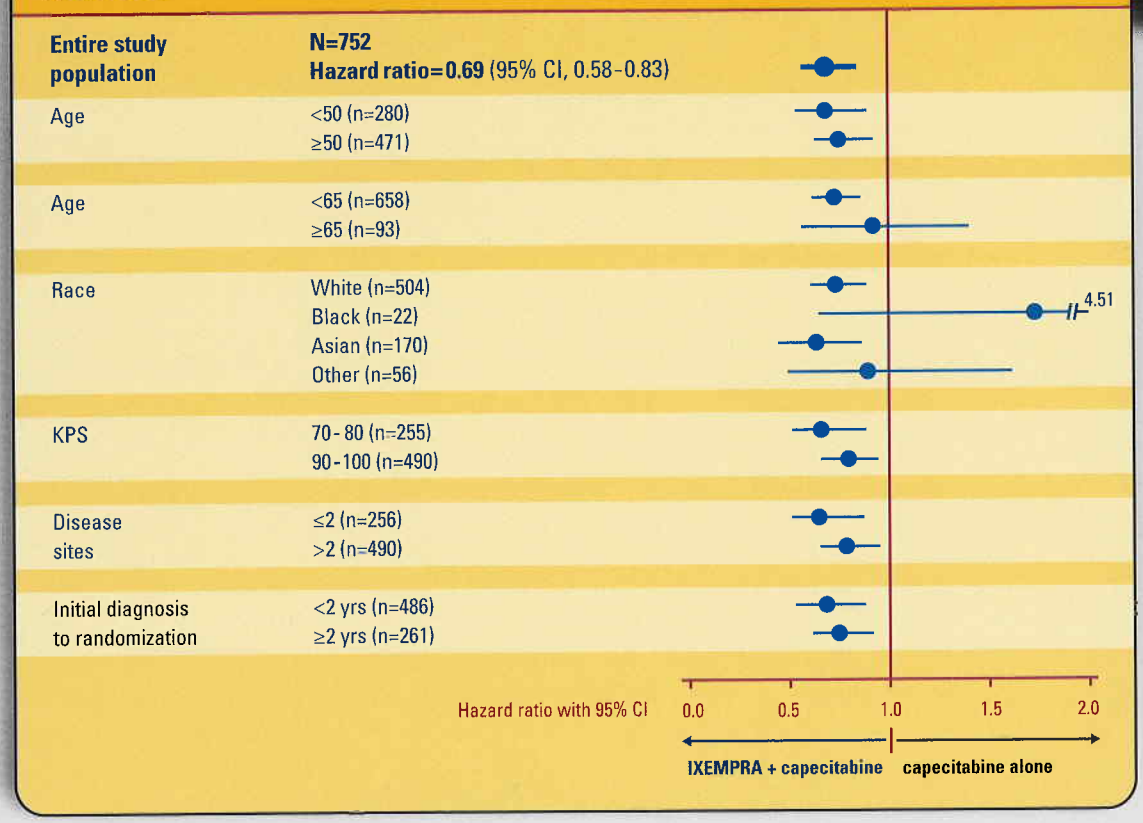
In MBC patients who have progressed on an anthracycline and a taxane

After the taxane fails,

Offer IXEMPRA® (ixabepilone) + capecitabine

Study 046: Consistent efficacy across patient subgroups[7]

IRR PFS hazard ratio and 95% CI for subset analyses



- A secondary analysis of PFS was conducted for the study population, based on potential prognostic factors, including age, race, KPS, number of disease sites (≤2, >2), preexisting liver dysfunction, visceral disease, anthracycline resistance, prior metastatic chemotherapy, and estrogen receptor status
- Most of the hazard ratios for IXEMPRA® (ixabepilone) were <1.0, suggesting consistent efficacy across subsets
- The hazard ratio for the black race was 1.72. For this subpopulation, low patient numbers (n=22) preclude interpretation of this result

IRR = independent radiologic review; PFS = progression-free survival; CI = confidence interval.

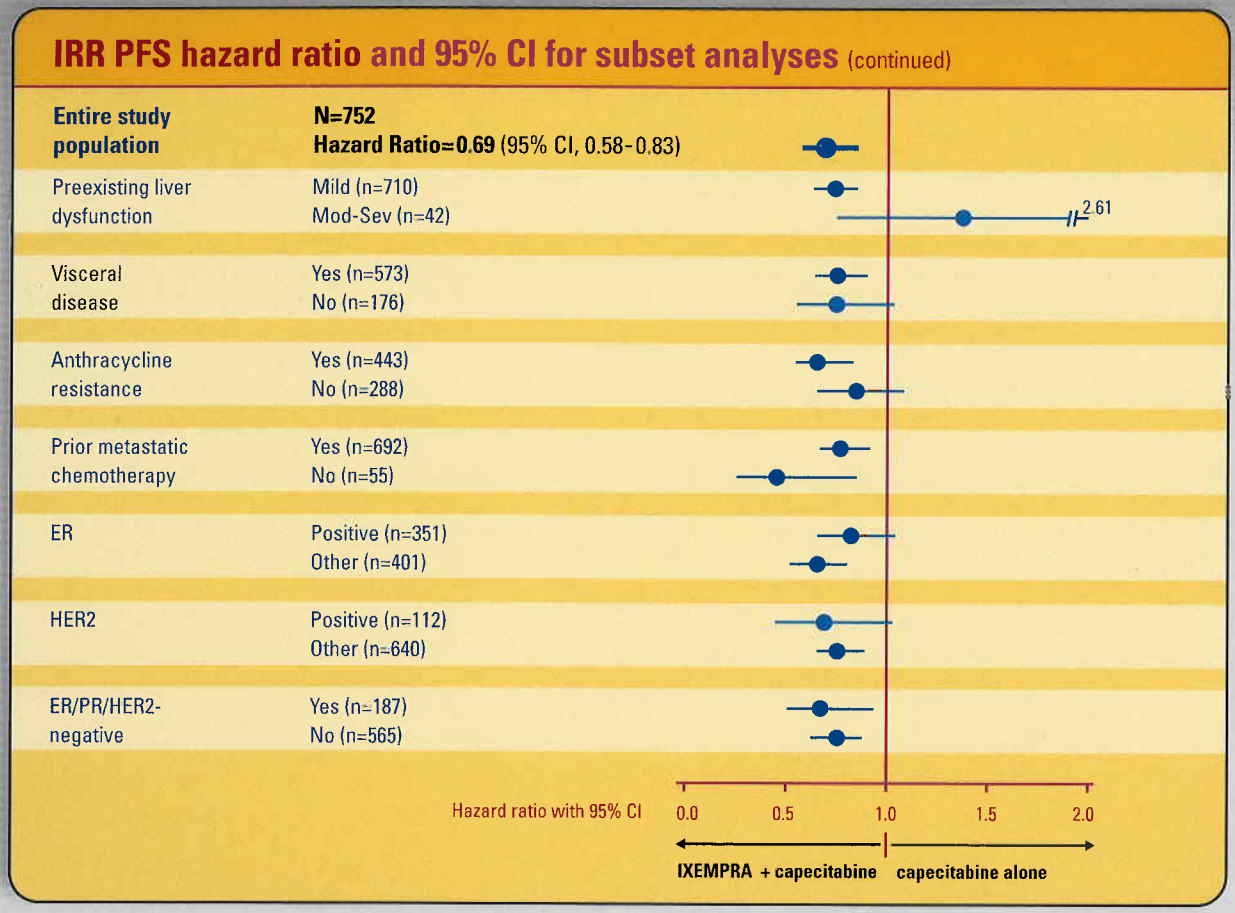
Safety Information: Pregnancy

- Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Study 046: Consistent efficacy across patient subgroups[7] (continued)

IRR PFS hazard ratio and 95% CI for subset analyses (continued)



- There was significant improvement in PFS, irrespective of HER2 expression, including patients with ER-negative/PR-negative/HER2-negative breast cancer, a disease subtype traditionally associated with poor prognosis
- The sample size for liver dysfunction was 42 patients. The increased hazard ratio for patients with moderate/severe hepatic dysfunction is consistent with increased risk of toxicity and neutropenia-related death. Treatment is contraindicated in this group[1]

Safety Information: Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA® (ixabepilone) should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

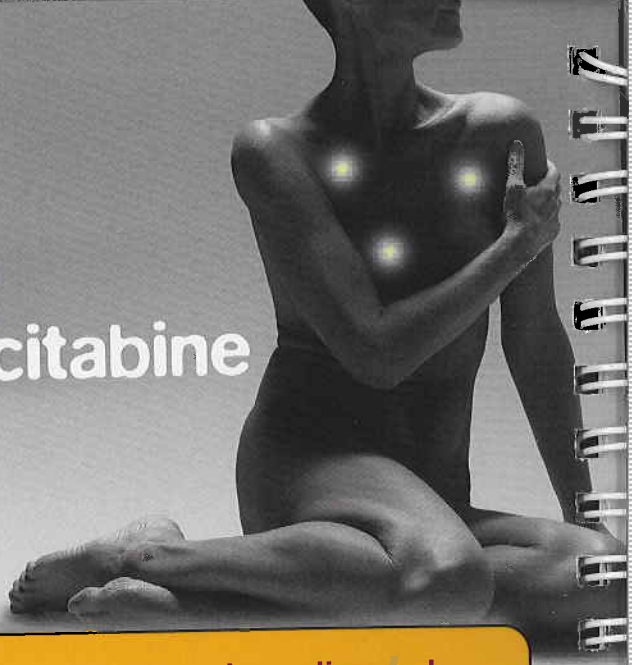
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection

In MBC patients who have progressed on an anthracycline and a taxane

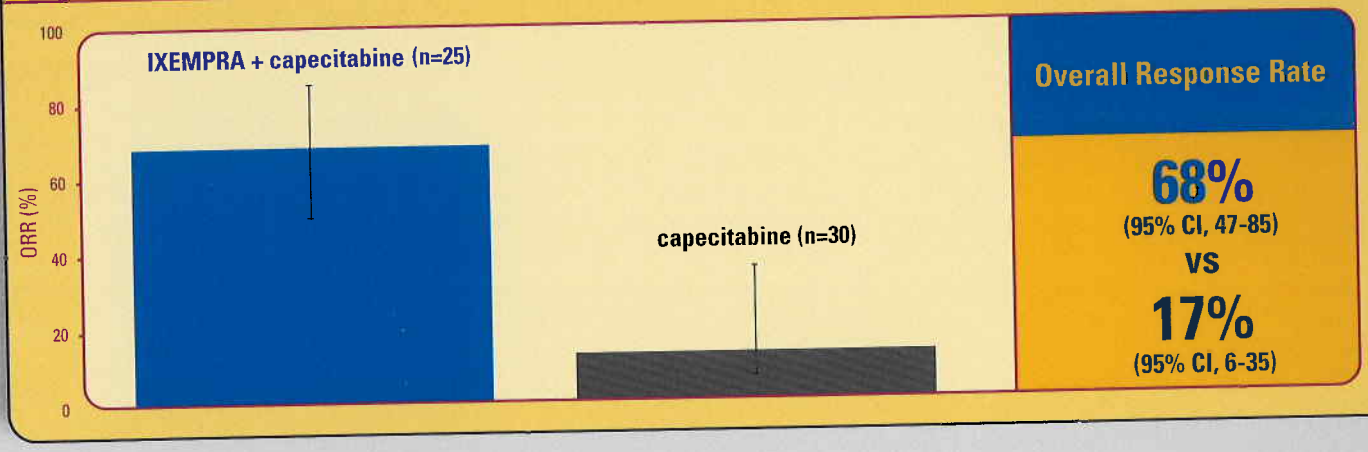
After the taxane fails,

Offer IXEMPRA® (ixabepilone) + capecitabine



Study 046: ORR within the prespecified analysis of 1st line patients[8]

Phase III trial results: ORR for patients who had relapsed ≤12 months after anthracyclines and taxanes in the adjuvant or neoadjuvant setting*[8]



- Study 046 included a prespecified analysis of patients who received study treatment as 1st line therapy. These were patients who had relapsed ≤12 months after anthracyclines and taxanes in the adjuvant or neoadjuvant setting and had received no prior treatments in the metastatic setting

Median PFS: 6.9 months (95% CI, 4.3-7.8) with IXEMPRA® (ixabepilone) plus capecitabine versus 2.7 months (95% CI, 1.5-4.2) with capecitabine alone (HR=0.42; 95% CI, 0.23-0.74)*

*ORR and PFS based on investigator assessment.

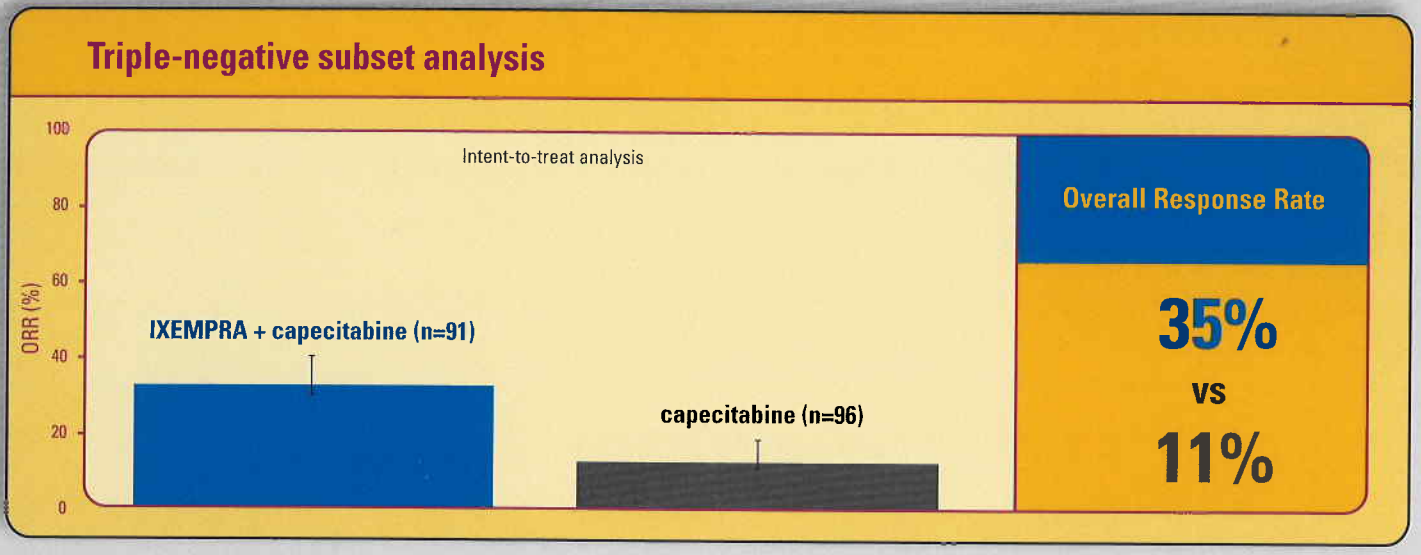
Safety Information: Myelosuppression

- IXEMPRA® (ixabepilone) must not be administered to patients with a neutrophil count <1500 cells/mm^3
- Myelosuppression is dose dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced
- Neutropenia-related death occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Study 046: ORR within the prespecified triple-negative subgroup[9]

IXEMPRA® (ixabepilone) + capecitabine demonstrated an ORR consistent with the overall population



Safety Information: Hepatic impairment

- Assessment of hepatic function is recommended before initiation of IXEMPRA® (ixabepilone) and periodically thereafter
- Patients with baseline AST or ALT >2.5 × ULN or bilirubin >1.5 × ULN experienced greater toxicity than patients with baseline AST or ALT ≤2.5 × ULN or bilirubin ≤1.5 × ULN when treated with IXEMPRA at 40 mg/m^2 in combination with capecitabine in breast cancer studies
- In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater

Safety Information: Cardiac adverse events

- Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group

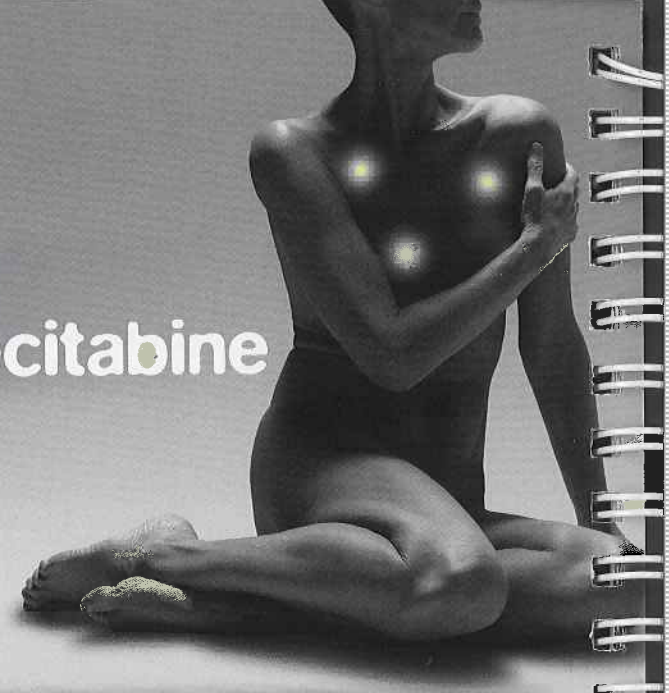
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™ (ixabepilone) for injection

In MBC patients who have progressed on an anthracycline and a taxane

After the taxane fails,

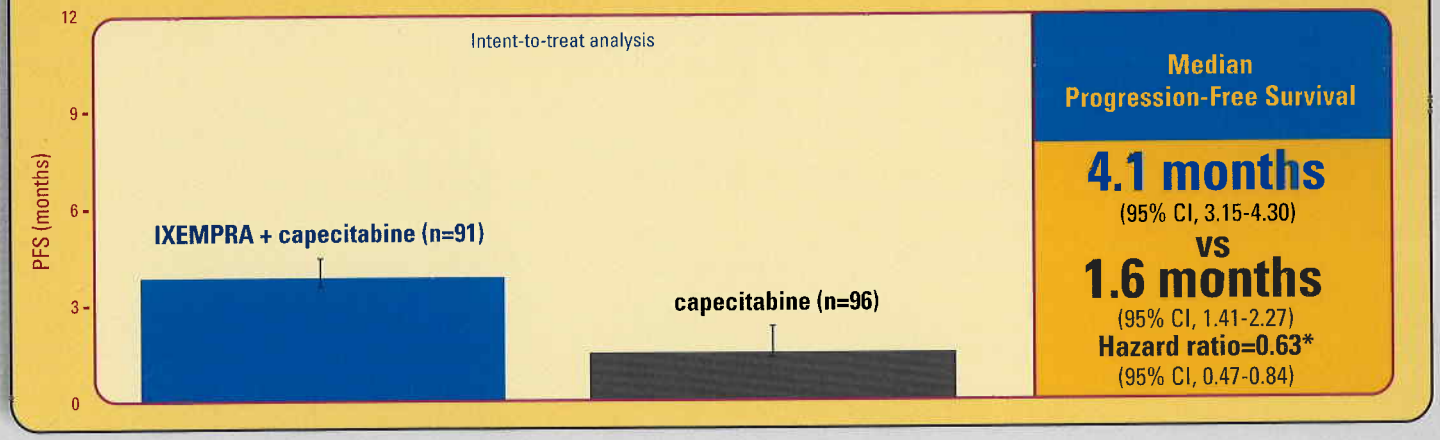
Offer IXEMPRA® (ixabepilone) + capecitabine



Study 046: PFS within the prespecified triple-negative subgroup[9]

IXEMPRA® (ixabepilone) + capecitabine provided an improvement in median PFS

Triple-negative subset analysis



*For the hazard ratio, a value less than 1.00 favors combination treatment.

Safety Information: Potential for cognitive impairment from excipients

- IXEMPRA® (ixabepilone) contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol

Safety Information: Adverse reactions in the overall population

- Treatment-related nonhematologic adverse events (≥20%) reported in patients treated with IXEMPRA in combination with capecitabine included: peripheral sensory neuropathy 65% (grade 3/4: 21%), palmar-plantar erythrodysesthesia (hand-foot) syndrome 64% (grade 3/4: 18%), fatigue/asthenia 60% (grade 3/4: 16%), nausea 53% (grade 3/4: 3%), diarrhea 44% (grade 3/4: 6%), vomiting 39% (grade 3/4: 4%), myalgia/arthralgia 39% (grade 3/4: 8%), anorexia 34% (grade 3/4: 3%), stomatitis/mucositis 31% (grade 3/4: 4%), alopecia 31% (grade 3/4: 0%), abdominal pain 24% (grade 3/4: 2%), nail disorder 24% (grade 3/4: 2%), musculoskeletal pain 23% (grade 3/4: 2%), and constipation 22% (grade 3/4: 0%). Treatment-related hematologic abnormalities (>40%) in Studies 081 and 046 included neutropenia, leukopenia, anemia, and thrombocytopenia. In Study 046, grade 3/4 hematologic adverse reactions included neutropenia 68%, leukopenia 57%, anemia 10%, and thrombocytopenia 8%

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

The safety profile of IXEMPRA® (ixabepilone) in combination with capecitabine

Study 046: Peripheral neuropathy[1]

Prior therapy with neurotoxic chemotherapy agents did not predict the development of neuropathy

- Peripheral neuropathy was common and primarily sensory

Peripheral neuropathy	
	IXEMPRA with capecitabine
Preexisting baseline neuropathy (grade 1)*	24%
Peripheral neuropathy (all grades)*	67%
Peripheral neuropathy (grade 3/4)*	23%
Median number of cycles to onset of neuropathy (grade 3/4)	4

*Sensory and motor neuropathy combined.

Peripheral neuropathy is cumulative, generally reversible, and should be managed with dose adjustments and delays

- The median time to improvement of grade 3/4 neuropathy to baseline or grade 1 was 6.0 weeks
- Following dose reduction, 80% of patients had improvement or no worsening of their neuropathy
- Discontinuation due to neuropathy was 21%

Safety Information: Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA® (ixabepilone) should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

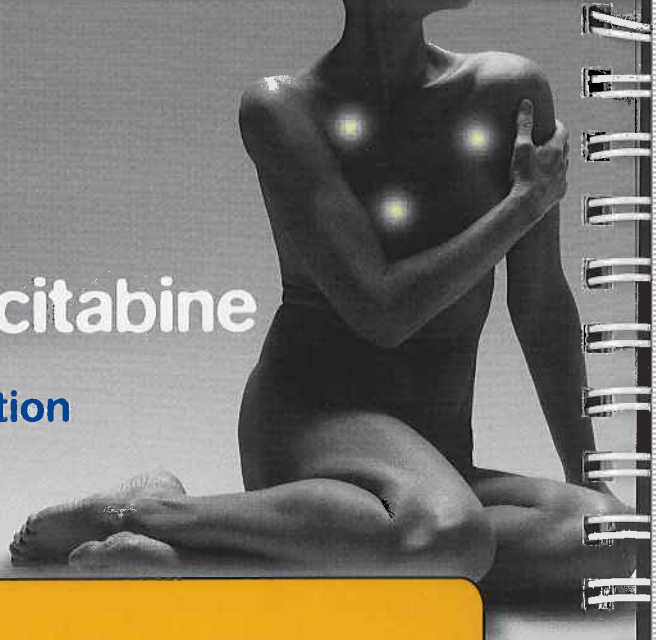
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection

In MBC patients who have progressed on an anthracycline and a taxane

After the taxane fails,

Offer IXEMPRA® (ixabepilone) + capecitabine



The safety profile of IXEMPRA in combination with capecitabine

Study 046: Hematologic abnormalities[1]

Hematologic abnormalities

	IXEMPRA + capecitabine (n=369)		capecitabine (n=368)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia*	32	36	9	2
Febrile neutropenia†‡	4	0	1	0
Leukopenia (WBC)	41	16	5	1
Anemia (Hgb)	8	2	4	1
Thrombocytopenia	5	3	2	2

*G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte-macrophage colony-stimulating factor) was used in 20% of patients who received IXEMPRA in Study 046.

†In clinical trials, febrile neutropenia was classified as a nonhematologic adverse event.

‡NCI CTC grading for febrile neutropenia ranges from grades 3 to 5. Three patients (1%) experienced grade 5 (fatal) febrile neutropenia. Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia.

- Infection with neutropenia was reported in 6% of patients treated with IXEMPRA® (ixabepilone) in combination with capecitabine

Safety Information: Myelosuppression

- IXEMPRA must not be administered to patients with a neutrophil count <1500 cells/mm^3
- Myelosuppression is dose dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced
- Neutropenia-related death occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine

Safety Information: Hepatic impairment

- Assessment of hepatic function is recommended before initiation of IXEMPRA and periodically thereafter
- Patients with baseline AST or ALT >2.5 × ULN or bilirubin >1.5 × ULN experienced greater toxicity than patients with baseline AST or ALT ≤2.5 × ULN or bilirubin ≤1.5 × ULN when treated with IXEMPRA at 40 mg/m^2 in combination with capecitabine in breast cancer studies
- In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

The safety profile of IXEMPRA® (ixabepilone) in combination with capecitabine

Study 046: Adverse reactions[1]

Adverse reactions occurring in ≥5% of patients

System organ class*/Preferred term	IXEMPRA + capecitabine (n=369) Total (%)	IXEMPRA + capecitabine (n=369) Grade 3/4 (%)	capecitabine (n=368) Total (%)	capecitabine (n=368) Grade 3/4 (%)
Infections and infestations				
Upper respiratory tract infection†	4	0	3	0
Blood and lymphatic system disorders				
Febrile neutropenia	5	4‡	1	1§
Immune system disorders				
Hypersensitivity†	2	1§	0	0
Metabolism and nutrition disorders				
Anorexia†	34	3§	15	1§
Dehydration†	5	2	2	<1§
Psychiatric				
Insomnia†	9	<1§	2	0
Nervous system disorders				
Peripheral neuropathy				
Sensory neuropathy†‖	65	21	16	0
Motor neuropathy†	16	5§	<1	0
Headache	8	<1§	3	0
Taste disorder†	12	0	4	0
Dizziness	8	1§	5	1§
Eye disorders				
Lacrimation increased	5	0	4	<1§
Vascular disorders				
Hot flush†	5	0	2	0
Respiratory, thoracic, and mediastinal disorders				
Dyspnea†	7	1	4	1
Cough†	6	0	2	0

*System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS).

†A composite of multiple MedDRA Preferred Terms.

‡NCI CTC grading for febrile neutropenia ranges from grade 3 to 5. Three patients (1%) experienced grade 5 (fatal) febrile neutropenia. Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia.

§No grade 4 reports.

‖Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyporeflexia, neuralgia, neuritis, neuropathy, neuropathy peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, pallanesthesia, peripheral sensory neuropathy, polyneuropathy, polyneuropathy toxic, and sensorimotor disorder. Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™ (ixabepilone) for injection

Study 046: Safety profile[1] (continued)

Adverse reactions occurring in ≥5% of patients

System organ class*/Preferred term	IXEMPRA + capecitabine (n=369) Total (%)	IXEMPRA + capecitabine (n=369) Grade 3/4 (%)	capecitabine (n=368) Total (%)	capecitabine (n=368) Grade 3/4 (%)
Gastrointestinal disorders				
Nausea	53	3†	40	2†
Vomiting‡	39	4†	24	2
Stomatitis/mucositis‡	31	4	20	3†
Diarrhea‡	44	6†	39	9
Constipation	22	0	6	<1†
Abdominal pain‡	24	2†	14	1†
Gastroesophageal reflux disease‡	7	1†	8	0
Skin and subcutaneous tissue disorders				
Alopecia‡	31	0	3	0
Skin rash‡	17	1†	7	0
Nail disorder‡	24	2†	10	<1†
Palmar-plantar erythrodysesthesia syndrome‡§	64	18†	63	17†
Pruritus	5	0	2	0
Skin exfoliation‡	5	<1†	3	0
Skin hyperpigmentation‡	11	0	14	0
Musculoskeletal, connective tissue, and bone disorders				
Myalgia/arthralgia‡	39	8†	5	<1†
Musculoskeletal pain‡	23	2†	5	0
General disorders and administrative site conditions				
Fatigue/asthenia‡	60	16	29	4
Edema‡	8	0	5	<1†
Pyrexia	10	1†	4	0
Pain‡	9	1†	2	0
Chest pain‡	4	1†	<1	0
Investigations				
Weight decreased	11	0	3	0

*System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS).

†No grade 4 reports.

‡A composite of multiple MedDRA Preferred Terms.

§Palmar-plantar erythrodysesthesia (hand-foot syndrome) was graded on a 1-3 severity scale in Study 046.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA® (ixabepilone) Dosing

For certain toxicities, an initial dose reduction of 20% is followed, on recurrence of toxicity, by an additional 20% dose reduction[1]

Depending on the type and severity of the toxicity, patients may require treatment discontinuation or no dose adjustment. If toxicities are present, treatment should be delayed to allow recovery.

The recommended dosage of IXEMPRA is 40 mg/m² administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m² should be calculated based on 2.2 m².

The dose of IXEMPRA is the same for monotherapy and for combination therapy with capecitabine.

Indications

IXEMPRA® (ixabepilone) is indicated as **monotherapy** for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

IXEMPRA is indicated in **combination** with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Warning: Toxicity in hepatic impairment

- **IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death.**

IXEMPRA™ (ixabepilone) for injection

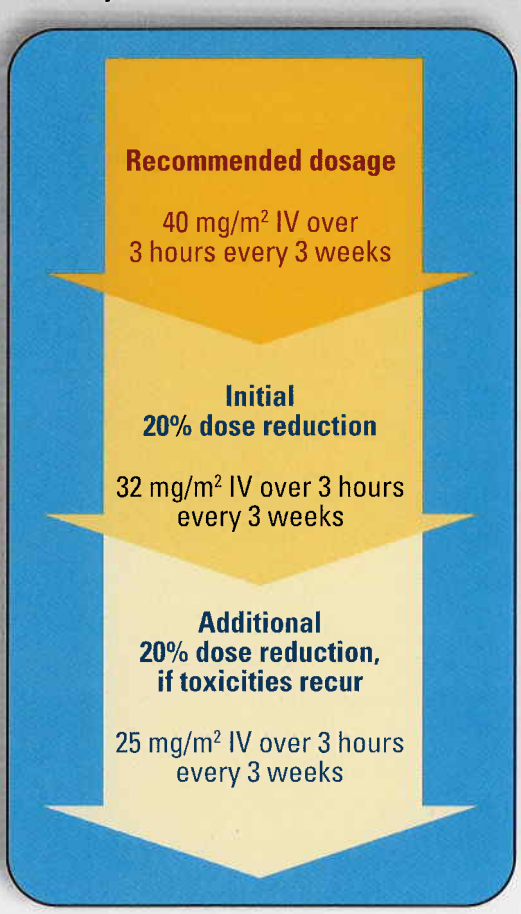
Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Dose modification[1]

For certain toxicities, an initial dose reduction of 20% is followed, on recurrence of toxicity, by an additional 20% dose reduction[1]

Patients should be evaluated during treatment by periodic clinical observation and laboratory tests, including complete blood cell counts. If toxicities are present, treatment should be delayed to allow recovery. General dosing adjustment guidelines for monotherapy and combination therapy are shown in the table below. Dose adjustments for specific toxicities are depicted on page 23. If toxicities recur, an additional 20% dose reduction should be made.

Dose adjustments for certain toxicities



Depending on the type and severity of the toxicity, patients may require treatment discontinuation or no dose adjustment. If toxicities are present, treatment should be delayed to allow recovery.

For patients who have hepatic impairment or use concomitant CYP3A4 inhibitors, please refer to pages 24 and 25.

- In Studies 046 and 081 respectively, 80% and 87% of patients with peripheral neuropathy who received IXEMPRA® (ixabepilone) had improvement or no worsening of their neuropathy following dose reduction[1]
- For patients with grade 3/4 neuropathy in Studies 046 and 081, 76% and 79%, respectively, had documented improvement to baseline or grade 1 neuropathy 12 weeks after onset[1]

Safety Information: Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Dose adjustments for toxicities*

IXEMPRA® (ixabepilone) (monotherapy or combination therapy)	Initial 20% IXEMPRA dose modification (32 mg/m²)	Additional 20% IXEMPRA dose modification (25 mg/m²), if toxicities recur
Nonhematologic		
Grade 2 neuropathy (moderate) lasting ≥7 days	Yes	Yes
Grade 3 neuropathy (severe) lasting <7 days	Yes	Yes
Grade 3 neuropathy (severe) lasting ≥7 days or disabling neuropathy	Discontinue treatment	
Any grade 3 toxicity (severe) other than neuropathy	Yes	Yes
Transient grade 3 arthralgia/myalgia or fatigue	No change in dose of IXEMPRA	
Grade 3 hand-foot syndrome (palmar-plantar erythrodysesthesia)	No change in dose of IXEMPRA	
Any grade 4 toxicity (disabling)	Discontinue treatment	
Hematologic		
Neutrophil <500 cells/mm³ for ≥7 days	Yes	Yes
Febrile neutropenia	Yes	Yes
Platelets <25,000/mm³ or platelets <50,000/mm³ with bleeding	Yes	Yes

*Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v3.0).

- If toxicities are present, treatment should be delayed to allow recovery

Capecitabine dose modifications for toxicities (when used in combination with IXEMPRA)

- For nonhematologic toxicities, follow the capecitabine label
- Hematologic toxicities:
  - For platelets <25,000/mm³ or platelets <50,000/mm³ with bleeding, hold for concurrent diarrhea or stomatitis until platelet count >50,000/mm³, then continue at same dose
  - For neutrophil count <500 cells/mm³ for ≥7 days or febrile neutropenia, hold for concurrent diarrhea or stomatitis until neutrophil count >1000 cells/mm³, then continue at same dose

Retreatment criteria

- Dose adjustments at the start of a cycle should be based on nonhematologic toxicity or blood counts from the preceding cycle following the guidelines above
- Patients should not begin a new cycle of treatment unless the neutrophil count is ≥1500 cells/mm³, the platelet count is ≥100,000 cells/mm³, and nonhematologic toxicities have improved to grade 1 (mild) or resolved

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™ (ixabepilone) for injection

Hepatically impaired patients[1]

- Assessment of hepatic function is recommended before initiation of IXEMPRA® (ixabepilone) and periodically thereafter
- Patients with baseline AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN experienced greater toxicity than patients with baseline AST or ALT ≤2.5 x ULN or bilirubin ≤1.5 x ULN when treated with IXEMPRA at 40 mg/m^2 in combination with capecitabine or as monotherapy in breast cancer studies

Toxicity in hepatic impairment

For combination therapy

- **IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN**
- Patients receiving combination treatment who have AST and ALT ≤2.5 x ULN and bilirubin ≤1 x ULN may receive the standard dose of IXEMPRA (40 mg/m^2)

For monotherapy

- Patients with hepatic impairment should be dosed with IXEMPRA based on the table below
- Patients with moderate hepatic impairment should be started at 20 mg/m^2; the dosage in subsequent cycles may be escalated up to, but not exceeding, 30 mg/m^2 if tolerated
- Use in patients with AST or ALT >10 x ULN or bilirubin >3 x ULN is not recommended
- Limited data are available for patients with AST or ALT >5 x ULN. Caution should be used when treating these patients

Dose adjustments for IXEMPRA as monotherapy in patients with hepatic impairment

	Transaminase levels		Bilirubin levels*	IXEMPRA (mg/m^2)†
Mild	AST and ALT ≤2.5 × ULN	and	≤1 × ULN	40
	AST and ALT ≤10 × ULN	and	≤1.5 × ULN	32
Moderate	AST and ALT ≤10 × ULN	and	>1.5 × ULN to ≤3 × ULN	20-30

*Excluding patients whose total bilirubin is elevated due to Gilbert's disease.

†Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Dose modifications for drugs that influence CYP3A4[1]

CYP3A4 inhibitors

- The use of concomitant strong CYP3A4 inhibitors should be avoided (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, or voriconazole)
- Grapefruit juice may also increase plasma concentrations of IXEMPRA® (ixabepilone) and should be avoided
- Based on pharmacokinetic studies, if a strong CYP3A4 inhibitor must be coadministered, a dose reduction to 20 mg/m^2 is predicted to adjust the IXEMPRA AUC to the range observed without inhibitors and should be considered
- If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the IXEMPRA dose is adjusted upward to the indicated dose
- Patients receiving CYP3A4 inhibitors during treatment with IXEMPRA should be monitored closely for acute toxicities (eg, frequent monitoring of peripheral blood counts between cycles of IXEMPRA)

CYP3A4 inducers

- The use of concomitant strong CYP3A4 inducers should be avoided (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital). Selection of an alternative concomitant medication with no or minimal enzyme induction potential should be considered
- The following guidance may be considered for dosing in patients requiring coadministration of a strong CYP3A4 inducer. Once patients have been maintained on a strong CYP3A4 inducer, the dose of IXEMPRA may be gradually increased from 40 mg/m^2 to 60 mg/m^2 depending on tolerance. If the dose is increased, IXEMPRA should be given as a 4 hour intravenous infusion. There are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. Patients whose dose is increased above 40 mg/m^2 should be monitored carefully for toxicities associated with IXEMPRA. If the strong inducer is discontinued, the IXEMPRA dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer
- St. John's wort may decrease plasma concentrations of IXEMPRA unpredictably and should be avoided

Overdosage[1]

- Experience with overdose with IXEMPRA is limited to isolated cases. The adverse reactions reported in these cases included peripheral neuropathy, fatigue, musculoskeletal pain/myalgia, and gastrointestinal symptoms (nausea, anorexia, diarrhea, abdominal pain, stomatitis). The highest dose mistakenly received was 100 mg/m^2 (total dose 185 mg)
- There is no known antidote for overdose of IXEMPRA. In case of overdose, the patient should be closely monitored and supportive treatment should be administered. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations

AUC = area under the curve.

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

IXEMPRA™
(ixabepilone) for injection

Use in special populations[1]

Geriatric use

- Clinical studies of IXEMPRA® (ixabepilone) did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently than younger subjects
- Forty-five of 431 patients treated with IXEMPRA in combination with capecitabine were ≥65 years of age and 3 patients were ≥75 years of age
- Overall, the incidence of grade 3/4 adverse reactions was higher in patients ≥65 years of age versus those <65 years of age (82% versus 68%) including grade 3/4 stomatitis (9% versus 1%), diarrhea (9% versus 6%), palmar-plantar erythrodysesthesia (hand-foot) syndrome (27% versus 20%), peripheral neuropathy (24% versus 22%), febrile neutropenia (9% versus 3%), fatigue (16% versus 12%), and asthenia (11% versus 6%)
- Toxicity-related deaths occurred in 2 (4.7%) of 43 patients ≥65 years of age with normal baseline hepatic function or mild impairment
- Thirty-two of 240 breast cancer patients treated with IXEMPRA as monotherapy were ≥65 years of age and 6 patients were ≥75 years of age. No overall differences in safety were observed in these patients compared to those <65 years of age

Renal impairment

- IXEMPRA is minimally excreted via the kidney
- No controlled pharmacokinetic studies were conducted with IXEMPRA in patients with renal impairment
- IXEMPRA in combination with capecitabine has not been evaluated in patients with calculated creatinine clearance of <50 mL/min
- IXEMPRA as monotherapy has not been evaluated in patients with creatinine >1.5 x ULN
- In a population pharmacokinetic analysis of IXEMPRA as monotherapy, there was no meaningful effect of mild and moderate renal insufficiency (CrCL >30 mL/min) on the pharmacokinetics of IXEMPRA

Pregnant women and nursing mothers

- IXEMPRA may cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies with IXEMPRA in pregnant women. Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- It is not known whether IXEMPRA is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IXEMPRA, a decision must be made whether to discontinue nursing or to discontinue IXEMPRA, taking into account the importance of the drug to the mother

Pediatric use

- The safety and effectiveness of IXEMPRA in pediatric patients have not been established

Please see Important Safety Information, including **boxed WARNING regarding hepatic impairment**, on pages 27 and 28.

Important Safety Information[1]

Toxicity in hepatic impairment

- **IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death**
- In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater in patients with hepatic impairment
- Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT >5 × ULN. Use of IXEMPRA in patients with AST or ALT >10 × ULN or bilirubin >3 × ULN is not recommended
- With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment

Contraindications

- IXEMPRA is contraindicated in patients:
  - with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives, such as polyoxyethylated castor oil
  - who have a baseline neutrophil count <1500 cells/mm^3 or a platelet count <100,000 cells/mm^3

Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

Myelosuppression

- Myelosuppression is dose-dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine. Neutropenia-related death occurred in 0.4% of 240 patients treated with IXEMPRA as monotherapy

Hypersensitivity reaction

- Premedicate with an H_1 and an H_2 antagonist approximately 1 hour before IXEMPRA infusion and observe for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started
- Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H_1 and H_2 antagonists, and extension of the infusion time should be considered

Cremophor is a registered trademark of BASF AG.
AST = aspartate aminotransferase
ALT = alanine aminotransferase
ULN = upper limit of normal
CTC = common terminology criteria

Continued on page 28.

Please see accompanying full Prescribing Information, including **boxed WARNING regarding hepatic impairment**, in pocket.

IXEMPRA™
(ixabepilone) for injection

Important Safety Information[1] (continued)

Pregnancy

- Women should be advised not to become pregnant when taking IXEMPRA® (ixabepilone). If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus

Cardiac adverse reactions

- Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group

Potential for cognitive impairment from excipients

- IXEMPRA contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol

Adverse reactions

Monotherapy

- The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA monotherapy were peripheral sensory neuropathy, 62% (grade 3/4: 14%); fatigue/asthenia, 56% (grade 3/4: 13%); myalgia/arthralgia, 49% (grade 3/4: 8%); alopecia, 48% (grade 3/4: 0%); nausea, 42% (grade 3/4: 2%); stomatitis/mucositis, 29% (grade 3/4: 6%); vomiting, 29% (grade 3/4: 1%); diarrhea, 22% (grade 3/4: 1%); and musculoskeletal pain, 20% (grade 3/4: 3%). Drug-associated hematologic abnormalities (>40%) included neutropenia, leukopenia, anemia, and thrombocytopenia. Grade 3/4 hematologic adverse reactions included neutropenia, 54%; leukopenia, 49%; anemia, 8%; and thrombocytopenia, 7%

Combination with capecitabine

- The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA in combination with capecitabine compared to capecitabine alone, respectively, were peripheral sensory neuropathy, 65% vs 16% (grade 3/4: 21% vs 0%); palmar-plantar erythrodysesthesia (hand-foot) syndrome, 64% vs 63% (grade 3/4: 18% vs 17%); fatigue/asthenia, 60% vs 29% (grade 3/4: 16% vs 4%); nausea, 53% vs 40% (grade 3/4: 3% vs 2%); diarrhea, 44% vs 39% (grade 3/4: 6% vs 9%); vomiting, 39% vs 24% (grade 3/4: 4% vs 2%); myalgia/arthralgia, 39% vs 5% (grade 3/4: 8% vs <1%); anorexia, 34% vs 15% (grade 3/4: 3% vs 1%); stomatitis/mucositis, 31% vs 20% (grade 3/4: 4% vs 3%); alopecia, 31% vs 3% (grade 3/4: 0% vs 0%); abdominal pain, 24% vs 14% (grade 3/4: 2% vs 1%); nail disorder, 24% vs 10% (grade 3/4: 2% vs <1%); musculoskeletal pain, 23% vs 5% (grade 3/4: 2% vs 0%); and constipation, 22% vs 6% (grade 3/4: 0% vs <1%). Drug-associated hematologic abnormalities (>40%) with IXEMPRA in combination with capecitabine and capecitabine alone, respectively, included neutropenia, leukopenia, anemia, and thrombocytopenia. Grade 3/4 hematologic adverse reactions included neutropenia, 68% vs 11%; leukopenia, 57% vs 6%; anemia, 10% vs 5%; and thrombocytopenia, 8% vs 4%

References: 1. IXEMPRA (ixabepilone) Prescribing Information. Bristol-Myers Squibb Company; Princeton, NJ. **2.** The NCCN Clinical Practice Guidelines in Oncology™ Breast Cancer (Version 2.2010). © 2009 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed May 5, 2010. **3.** Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol.* 2007;25(23):3407-3414. **4.** Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Nat Cancer Inst.* 2000;92(3):205-216. **5.** Data on file: IXEM002. Study CA163081. Bristol-Myers Squibb: Princeton, NJ; 2009. **6.** Data on file: IXEM001a. Bristol-Myers Squibb: Princeton, NJ; 2009. **7.** Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol.* 2007;25(33):5210-5217. **8.** Vahdat L, Fein LE, Karwal MW, et al. Ixabepilone plus capecitabine vs capecitabine in patients with metastatic breast cancer receiving ixabepilone in the first line setting: a pooled analysis from two phase III studies. Poster presented at the San Antonio Breast Cancer Symposium. Dec. 12, 2008. Poster Number 6117. **9.** Rugo HS, Roche H, Thomas E, et al. Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. Poster presented at the San Antonio Breast Cancer Symposium. Dec. 12, 2008. Poster Number 3057.

Please see accompanying full Prescribing Information, including **boxed WARNING regarding hepatic impairment**, in pocket.

For additional information, please call 1-888-IXEMPRA (493-6772) or visit www.IXEMPRA.com.

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Bristol-Myers Squibb

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IXEMPRA™ (ixabepilone) for injection

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XEMPRA™

abepilone) for injection

Kelly*
Age: 51 years

DIAGNOSIS

INITIAL STAGE:

— 3.0 cm, 5 positive lymph nodes, Stage 3

HER2/HORMONAL STATUS:

— HER2-, ER-, PR-

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2) + cyclophosphamide + a taxane

— Time to progression/relapse from adjuvant = 18 months

1ST LINE METASTATIC CHEMOTHERAPY:

— Taxane + bevacizumab (progressed on therapy after 9 months)

PRESENTATION

GENERAL:

— Caring for self, not capable of normal activity or work

SITES OF METASTASES:

— Multiple liver lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

Kelly*
Age: 51 years

DIAGNOSIS

INITIAL STAGE:

— 3.0 cm, 5 positive lymph nodes, Stage 3

HER2/HORMONAL STATUS:

— HER2-, ER-, PR-

SYSTEMIC TREATMENT HISTORY

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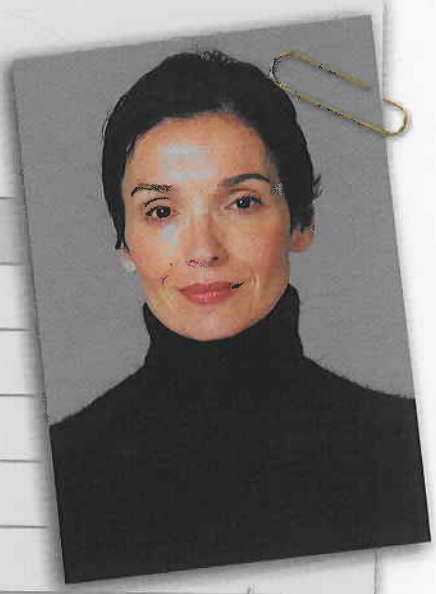
XEMPRA™

abepilone) for injection

Fay*
Age: 42 years



DIAGNOSIS

INITIAL STAGE:

— 2.0 cm tumor,

2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER+, PR-

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)

+ cyclophosphamide + a taxane

— Time to progression/relapse from adjuvant =

10 months while on endocrine therapy

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty;

some symptoms or signs of disease

SITES OF METASTASES:

— Multiple liver lesions and bone lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

Fay*
Age: 42 years

DIAGNOSIS

INITIAL STAGE:

— 2.0 cm tumor,
2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER+, PR-

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)
+ cyclophosphamide + a taxane

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PRESENTATION

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SITES OF METASTASES:

— Multiple liver lesions and bone lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

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XEMPRA™
xabepilone) for injection

Mary*
Age: 62 years

DIAGNOSIS

INITIAL STAGE:

— 2.3 cm, 2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER+, PR+

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)
+ cyclophosphamide + a taxane

— 5 years of endocrine therapy

— Time to progression/relapse from adjuvant = 7 years

PROGRESSED ON ENDOCRINE THERAPY
IN THE METASTATIC SETTING

1ST LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 10 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Nab-paclitaxel (progressed on therapy after 8 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty; some symptoms or signs of disease

SITES OF METASTASES:

— Bone and liver lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

Mary*
Age: 62 years

DIAGNOSIS

INITIAL STAGE:

— 2.3 cm, 2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER+, PR+

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)

+ cyclophosphamide + a taxane

— 5 years of endocrine therapy

— Time to progression/relapse from adjuvant = 7 years

PROGRESSED ON ENDOCRINE THERAPY
IN THE METASTATIC SETTING

1ST LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 10 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Nab-paclitaxel (progressed on therapy after 8 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty;

some symptoms or signs of disease

SITES OF METASTASES:

— Bone and liver lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

Jane*
Age: 57 years

DIAGNOSIS

INITIAL STAGE:

— 1.2 cm, lymph node negative, Stage 1

HER2/HORMONAL STATUS:

— HER2-, ER+, PR+

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)

+ cyclophosphamide

— 5 years of endocrine therapy

— Time to progression/relapse from adjuvant = 6 years

PROGRESSED ON ENDOCRINE THERAPY IN THE METASTATIC SETTING

1ST LINE METASTATIC CHEMOTHERAPY:

— Taxane + bevacizumab (progressed on therapy after 12 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 7 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty; some symptoms or signs of disease

SITES OF METASTASES:

— Bone and lung lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

IXEMPRA™
xabepilone) for injection

Jane*
Age: 57 years

DIAGNOSIS

INITIAL STAGE:

— 1.2 cm, lymph node negative, Stage 1

HER2/HORMONAL STATUS:

— HER2-, ER+, PR+

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2)

+ cyclophosphamide

— 5 years of endocrine therapy

— Time to progression/relapse from adjuvant = 6 years

PROGRESSED ON ENDOCRINE THERAPY
IN THE METASTATIC SETTING

1ST LINE METASTATIC CHEMOTHERAPY:

— Taxane + bevacizumab (progressed on therapy after 12 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 7 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty;

some symptoms or signs of disease

SITES OF METASTASES:

— Bone and lung lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

Sarah*
Age: 45 years

DIAGNOSIS

INITIAL STAGE:

— 2.5 cm, 2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER-, PR-

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2) + cyclophosphamide + docetaxel

— Time to progression/relapse from adjuvant = 24 months

1ST LINE METASTATIC CHEMOTHERAPY:

— Received a taxane + bevacizumab (progressed on therapy after 12 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 5 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty; some symptoms or signs of disease

SITES OF METASTASES:

— Liver and lung lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.

IXEMPRA™
xabepilone) for injection

Sarah*
Age: 45 years

DIAGNOSIS

INITIAL STAGE:

— 2.5 cm, 2 positive lymph nodes, Stage 2

HER2/HORMONAL STATUS:

— HER2-, ER-, PR-

SYSTEMIC TREATMENT HISTORY

ADJUVANT:

— Doxorubicin (cumulative dose of 240 mg/m^2) + cyclophosphamide + docetaxel

— Time to progression/relapse from adjuvant = 24 months

1ST LINE METASTATIC CHEMOTHERAPY:

— Received a taxane + bevacizumab (progressed on therapy after 12 months)

2ND LINE METASTATIC CHEMOTHERAPY:

— Capecitabine (progressed on therapy after 5 months)

PRESENTATION

GENERAL:

— Patient has normal activity with some difficulty; some symptoms or signs of disease

SITES OF METASTASES:

— Liver and lung lesions

PERTINENT LABS:

— Normal liver/kidney function and normal CBCs

*Hypothetical patient profile. Photo not of actual patient.